

Monitoring of myocardial function by epicardial ultrasonic transducers.



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Abbreviations

2D	two-dimensional (echocardiography)
$3,5\tau/DD$	complete relaxation as fraction of diastolic duration
A	transmitral filling wave (late diastole)
a'	wall thinning velocity (late diastole)
E	transmitral filling wave (early diastole)
e'_{wt}	wall thinning velocity (early diastole)
ESS	end systolic stress
ECG	electrocardiogram
IMA	internal mammary artery
LAD	left anterior descending coronary artery
LV	left ventricle
$LVdP/dt$	time derivative of left ventricular pressure
LVP	left ventricle pressure
mFS	midwall fractional shortening
OPCAB	off-pump coronary artery bypass grafting
PSV	post-systolic wall thickening velocity
P-WT	pressure-wall thickness (loops)
S'	systolic wall thickening velocity
τ	relaxation constant
TDI	tissue Doppler imaging
V_{diff}	$= PSV - S'$

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Oslo, May 2013

Publications

Paper I

Espinoza A, Halvorsen PS, Hoff L, Skulstad H, Fosse E, Ihlen H, Edvardsen T. Detecting myocardial ischaemia using miniature ultrasonic transducers – a feasibility study in a porcine model. *Eur J Cardiothorac Surg* 2010; 37: 119-126.

Paper II

Espinoza A, Kerans V, Opdahl A, Skulstad H, Halvorsen P S, Bugge JF, Fosse E, Edvardsen T. Effects of therapeutic hypothermia on left ventricular function assessed by ultrasound imaging. *Accepted for publication in J Am Soc Echocardiography (2013)*

Paper III

Espinoza A, Halvorsen PS, Skulstad H, Lundblad R, Bugge JF, Hoff L, Fosse E, Edvardsen T. Automated detection of myocardial ischaemia by epicardial miniature ultrasound transducers – a novel tool for patient monitoring during cardiac surgery. *Eur J Cardiothorac Surg* 2011; 39: 53-59

Introduction

The number of elderly patients undergoing cardiac surgery has increased in recent years. These patients often present with significant comorbidity, and thereby carry a higher risk of adverse outcome.¹ The occurrence of myocardial ischemia in the perioperative setting predicts worsened outcome for the patients.² Early detection, and correction of the underlying cause - if possible - is therefore of great importance.

The use of continuous ECG monitoring, automated ST segment analysis, and assessment of hemodynamic variables are routinely used to detect myocardial ischemia in the perioperative setting during cardiac and non-cardiac surgery. However, the sensitivity of these methods regarding identification of myocardial ischemia and myocardial dysfunction is variable. The use of echocardiography for detection of wall motion abnormalities has proved more sensitive than use of conventional hemodynamic and ECG monitoring alone.³⁻⁵ The echocardiographic detection of wall motion abnormalities is of great importance, since the occurrence of these during and after cardiac surgery have been shown to predict poor patient outcome.^{6,7}

Ultrasound imaging

The use of ultrasound to present images of cardiac motion was described first in 1954.⁸ The primordial ultrasonic technique used a pulse-echo distance ranging signal photographed on a running film to produce the first crude M-mode image. Over the next decades the technique improved, but live 2D images of the heart from reasonable sized machines did not emerge until the mid 1970's. Since then technical advancement have made vast improvements in imaging quality, and addition of color imaging techniques to visualize blood flow and tissue velocities has expanded the diagnostic opportunities. This makes echocardiography one of the mainstay diagnostic modalities in present cardiology.

New echocardiographic techniques have evolved in recent years, such as tissue Doppler imaging (TDI), and strain echocardiography.^{9,10} These techniques have improved quantification of myocardial function at segmental level by tissue velocity and strain, and they have demonstrated improved sensitivity for detection of ischemia compared to regional wall motion assessment.¹¹⁻¹⁴ These techniques also have enabled a more

detailed study of the myocardial segmental motion related to timing of the cardiac cycle, and the inclusion of pre- and post-ejection velocities together with ejection velocity have resulted in improved sensitivity in ischemia detection.¹⁵ Both tissue Doppler velocity and strain echocardiography have proved useful in the setting of cardiac surgery.^{16,17}

The use of ultrasonic transducers for placement on the epicardium, or in the myocardium was introduced in 1956 when a two-crystal technique was described, where one crystal served as transmitter and the other as receiver.¹⁸ The distance between them was measured through the cardiac cycle as an expression of myocardial function. In the following years important contributions to the understanding of cardiac physiology were made using this technique.^{19,20} The two-crystal technique was used also for wall thickness studies, but in 1983 a single-crystal technique was introduced for this purpose, where the crystal alternately acted as transmitter and receiver.²¹ This Doppler method used an audio signal for guiding the sample volume to a depth that would allow subendocardial velocity sampling through the cardiac cycle, which in turn presented a curve of the estimated wall thickness.

The visualization of the cardiac function provides valuable information that can not be achieved by use of hemodynamic or electrocardiographic monitoring. The efforts to provide a continuous imaging method, particularly for use in the setting of cardiac surgery, have produced several technologies. The use of intracardiac ultrasound probes, and the more elaborate placement of a 2D imaging scanner on the epicardial surface for in-situ monitoring in the per- and post-operative phase have been described, although the latter has not gained further use.^{22,23}

Assessment of myocardial function in cardiac surgery

The surgical repertoire has evolved in the recent years, and more complex cardiac surgery procedures are performed. The planning of such procedures are guided by more recent imaging techniques in the preoperative evaluation, using advanced echocardiography, CT and MR. In the same period the population presenting for surgery have increased in age and load of comorbidity. Thus, the management of the cardiac

surgery patients represents an increasing challenge during the perioperative course, while development in monitoring techniques has not changed similarly.

ECG and hemodynamic monitoring are routinely used for guiding management of patients during cardiac surgery. These modalities are readily available and are displayed continuously on bedside monitors. ST segment analysis also has the advantage that it can be provided automatically. However, these modalities present reflections of cardiac function, and do not necessarily reveal impaired function, i.e. myocardial dysfunction may occur without changes in ECG or hemodynamics.²⁴ Central hemodynamic monitoring by use of the pulmonary artery catheter, or pulse contour analysis, provide information on global cardiovascular function, and is often used in advanced patient monitoring. Even though these techniques provide important information, they are global cardiovascular monitoring devices, and due to lack of sensitivity may display normal values in the presence of severe myocardial dysfunction.^{17,25,26} In the cited patient studies normal cardiac output values were measured during occlusion of major coronary vessels. This might be due to time lag in presentation, or because the cardiac output techniques were not sensitive in detection of regional myocardial dysfunction.

Peroperative echocardiography is increasingly used in cardiac surgery patients. This gives immediate information on the result of the surgical repair, but is also used to evaluate the myocardial function. The drawback is that the technique requires a skilled operator for image acquisition and interpretation, and echocardiography examination is still performed intermittently. Moreover, the advanced analysis of echocardiography Tissue Doppler velocity or strain echocardiography is performed off-line. A method is warranted that could provide continuous myocardial function, and not only indirect measures of cardiovascular function, to support decision making and individualization of hemodynamic management in the perioperative setting.

Based on the superiority of echocardiography to assess myocardial function and detection of ischemia, and the recent evolution of more sensitive ultrasound monitoring principles, the work to make an ultrasonic system that could provide continuous assessment commenced at The Intervention Centre in 2006. The intention was to construct miniature ultrasonic transducers that could be sutured on the surface of the

heart, and further could be connected to a unit that would display the signal continuously, and in real-time. The signal would be presented as a conventional M-mode image, and provide quantification of myocardial performance.

The testing and validation of the ultrasonic system was performed in two experimental animal models and in one clinical study. The experimental models allowed assessment of the myocardial systolic and diastolic function by the use of epicardial ultrasound signals in response to relevant physiological and pharmacological challenges, as well as different grades of regional function impairment. The clinical study was performed in patients undergoing coronary bypass surgery without the use of cardiopulmonary bypass. This enabled validation of the system's ability to detect regional function impairment due to ischemia in a clinical setting. This also opened for validation of an operator independent algorithm for automated signal analysis that could be used as a bedside monitoring tool.

Aims of the study

The aims of this study were

1. to provide an advanced ultrasonic system with miniaturized transducers that could be placed on the surface of the heart; and that could be used for continuous monitoring of myocardial function in the perioperative phase during cardiac surgery.
2. to explore the use of systolic and diastolic myocardial function indices obtained by the new system for evaluation of global and regional myocardial function, and to extract signals that could discriminate regional myocardial dysfunction from global changes in myocardial function.
3. to validate the ability of the ultrasonic system to detect changes in regional myocardial function in patients with pre-existing coronary disease, and
4. to validate algorithms for automated analysis of the signal that could differentiate regional dysfunction from global myocardial dysfunction, and would facilitate automated signal interpretation in a bedside setting.
5. By use of ultrasound imaging techniques to study the changes in myocardial performance when exposed to moderate hypothermia.

Material and methods

The evaluation of the continuous epicardial ultrasound system was performed in two experimental studies (I and II) and one clinical study (III). The experimental studies were designed to evaluate the ultrasonic system and its ability to assess systolic and diastolic myocardial function during global and regional cardiovascular changes that are clinically relevant.

Experimental studies

Two experimental studies were performed with eight animals (Norwegian land race pigs) included in study I, and ten in study II. The studies were approved by the National Animal Research Authority, and all animals were handled according to national and international regulations.²⁷ The anatomy of the porcine heart and its coronary supply is comparable to that of humans, and allowed similar placement of the ultrasonic sensors in all experiments. In addition, the size of the porcine model facilitated the elaborate instrumentation in both studies without compromising cardiac function. The details of anesthesia and surgical preparation are described in paper I and II, some key points are included below

Global interventions

Global interventions were made to provide changes in cardiovascular function similar to those that may appear in the perioperative course of cardiac surgery. Changes in loading conditions were induced by volume infusion and by use intravenous infusion of nitroprusside for pharmacological unloading. Adrenergic stimulation and blocking were made by use of intravenous administration of epinephrine and esmolol (Study I). These drugs inflict changes at several “targets” in the cardiovascular system, e.g. epinephrine induces changes not only in myocardial contractile function. Nevertheless, these interventions represent relevant challenges or therapeutic strategies in the perioperative setting.

Hypothermia is used during cardiac surgery for neuroprotection and myocardial preservation. The patients undergoing cardiac surgery may be incompletely rewarmed

before they are weaned from cardiopulmonary bypass, and a resulting temperature afterdrop may represent a challenge regarding cardiac function.²⁸ Hypothermia is also used to improve outcome in comatose survivors of out-of-hospital cardiac arrest.^{29,30} The cardiac function in these patients can be severely reduced, and circulatory support may be required.³¹ Thus, both in the cardiac surgery patients and in the post-cardiac arrest patients the myocardial function may be impeded both by the insult to the myocardium and from the induced hypothermia.

To study the effects from hypothermia *per se* on cardiac function, the animals in Study II were cooled to 33° C. This is a temperature level often used during cardiac surgery and in therapeutic hypothermia after cardiac arrest. Systolic and diastolic function indices during hypothermia were compared to the same indices during normothermia.

In the hypothermia study (Study II) the animals were anesthetized using inspired isoflurane and morphine infusion, without the routine use of muscle relaxing agents. The avoidance of muscle relaxants was intended in order to detect shivering or other signs of inadequate anesthesia that could infer an increase in cardiac demands.³² Hypothermia was induced by use of an intravascular cooling catheter placed in the inferior vena cava. The choice of cooling modality was mainly determined by practical considerations. The use of water-circulated surface-cooling pads is routinely used for therapeutic hypothermia in ICU settings. However, in a porcine model the available surface would be reduced due to the lesser surface-volume ratio in the pig compared to humans, and because of the open chest nature of our model. It has been speculated whether internal cooling would reduce the incidence of shivering compared to surface cooling, but recent studies have not been able to confirm this.³³

Measurements on systolic and diastolic function were obtained by 2D echocardiography and by the epicardial ultrasound transducers. Micro-manometer tipped catheters were placed in the left ventricle cavity, and wall dimensions were plotted against LV pressure through the cardiac cycle to obtain pressure-wall thickness loops (see section on Systolic and diastolic function indices).

Recordings were made at baseline temperature (38° C) and during hypothermia (33° C) at spontaneous heart rate. Four of the animals were initially cooled for measurements

during hypothermia, before they were rewarmed and repeated measurements were made at normothermia.

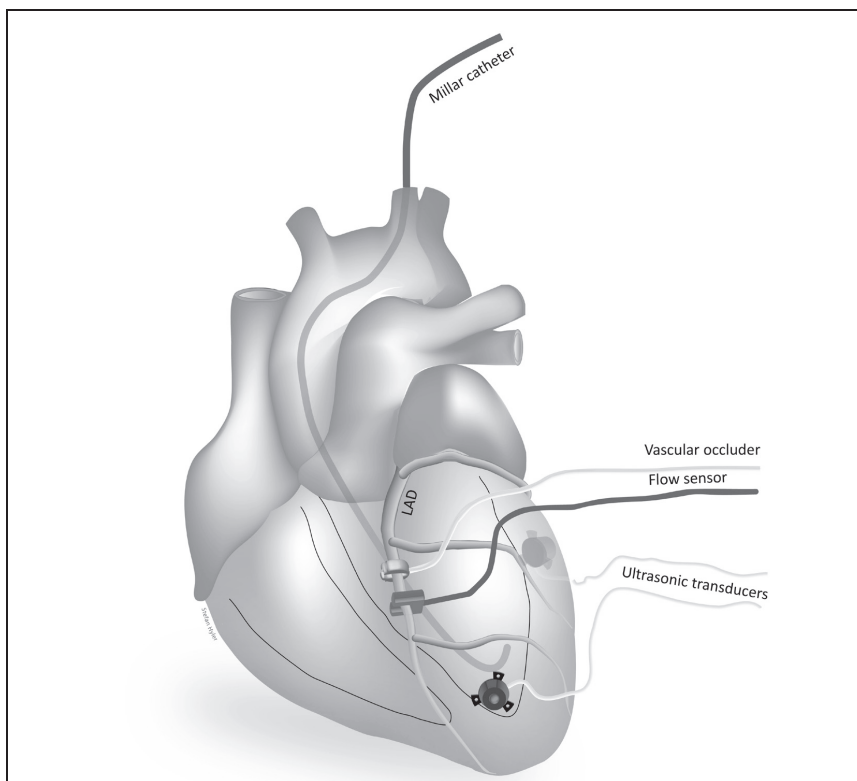


Figure 1. Illustration of the placement of two ultrasonic sensors on the heart; one placed in the region downstream of the vascular occluder on the LAD, and the other basolaterally of the 1st diagonal branch. (Ill: S. Hyler)

Regional interventions

The regional intervention in study I was made by transient occlusion of the LAD. Graded flow reduction in LAD was performed in a subgroup (six of eight animals) to investigate the ability of the sensor system to detect changes in myocardial performance due to smaller changes in blood supply. This would mimic the scenario of partial reduction in coronary or graft flow. The ultrasound transducer was fixated to the anterior left ventricular wall in the left anterior descending coronary artery (LAD)

supply area, the region most frequently grafted in coronary artery bypass (CAB) surgery. The anatomy gave room to fit both a vascular occluder and flow measurement probe on the LAD distal of the 1st diagonal branch. To assess the ability of the sensor system to detect regional changes, another ultrasound transducer was placed in a basolateral reference region up-stream of the 1st diagonal branch (Figure 1).

Clinical study

Ten patients undergoing off-pump coronary artery bypass grafting (OPCAB) were included in the study (Paper III). The study was approved by The Regional Committee for Medical Research Ethics of Southern Norway. All patients gave written consent. The details of surgical preparation and monitoring set-up are described in paper III.

In conventional coronary bypass surgery the patient is connected to a cardiopulmonary bypass machine that pumps oxygenated blood to the body, in order to allow surgery on the arrested heart. During OPCAB the heart is beating and the blood supply to the myocardium depends on coronary artery flow. When performing the bypass, the coronary vessel is temporarily occluded during the anastomotic suturing. In our study this provided an experiment-like situation where changes in flow and function in the interventional region could be measured within short intervals.

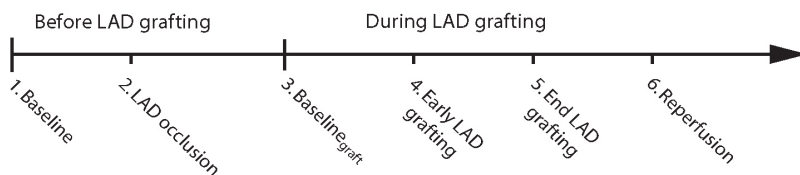


Figure 2. Time line for the registrations before and during LAD grafting. (From Espinoza et al. *Eur J Cardiothorac Surg* 2011(39):53-56)

Two ultrasound transducers were sutured to the epicardium, one in the LAD supply area, and one for reference in the basolateral region of the anterior left ventricular wall, the latter region not supplied by the distal LAD (Figure 1). Occlusion of LAD was

performed two times. The first occlusion was made after pericardiotomy, before the heart was positioned for surgery. Reperfusion was allowed for 5 minutes before subsequent positioning for LAD surgery. The second LAD occlusion was made during grafting of the internal mammary artery (IMA) to the LAD. The use of intracoronary shunt during IMA-to-LAD grafting was made at the surgeon's discretion.

Miniature epicardial transducer recordings were made with echocardiography measurements for reference during trial occlusion of LAD, and after completed bypass surgery before chest closure (Time points 1, 2 and 6 in Figure 2). In addition miniature transducer recordings were made during LAD grafting (Time points 3, 4 and 5). ECG and blood pressure traces were obtained from the patient monitor, and were recorded together with the ultrasonic recordings from the epicardial transducers.

Epicardial ultrasonic system

The ultrasonic elements were custom-made for these studies (Imasonic SA, Besançon, France). They consisted of 10 MHz single element transducers encapsulated in biocompatible polymer housing with eyes for suture fixation to the epicardium. This would ensure a perpendicular insonation angle on the left ventricular wall in all situations. The porcine model had comparable cardiac dimensions and wall thickness to that of adult humans. Hence, the focal distance of 20 mm permitted use of similar transducers in both experimental and patient studies. The transducers were connected to an analogue transmitter-receiver system, with two channels for use of the two transducers simultaneously. The transmit pulses were routed to the transducers simultaneously; the received echoes were separated and routed to an amplifier (*AD8332-EVALZ*, Analog Devices Inc., Norwood, Massachusetts, USA). For use in the patient study, the modified transducers were separated from the image acquisition equipment by ferrite rings, to provide galvanic insulation for patient safety.

The signals were sampled by software written in LabVIEW (National Instruments Corp., Austin, Texas, USA) and were presented in real-time as M-mode images with corresponding wall thickening velocities. Signal recording was made with synchronized ECG and pressure signals on a desktop computer, for off-line analysis.³⁴

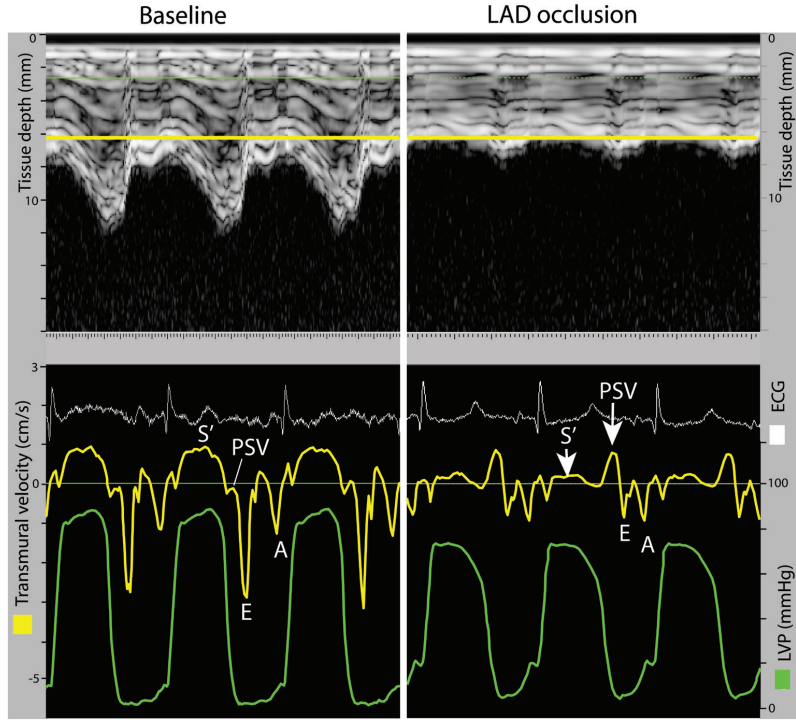


Figure 3. The figure displays the M-mode images from the region of intervention in study I (LAD coronary artery supply region). Recordings are shown at baseline (left) and during occlusion of the LAD (right panel). Placements of sample volumes for wall thickening velocities are shown as yellow lines in the M-mode images. The velocity traces shown in the lower panels were synchronized with ECG and left ventricular pressure (LVP). Wall thickening is reduced during LAD occlusion, and wall thickening velocity demonstrates reduction in systolic velocity (S') and increase in post-systolic velocity (PSV). E and A indicates early and late diastolic wall thinning velocities, respectively. (Modified from Espinoza et al. Eur J Cardiothorac Surg 2010 (37):119-26)

The M-mode recordings provided an instantaneous transmural image of the myocardial wall. Guided by these images the appropriate depth for wall thickening velocities was chosen, ensuring positioning of the sample volume within the myocardium through the cardiac cycle. When the wall was stretched in diastole the sample volume would be just beneath the endocardium; during wall thickening in systole the sample volume would be

farther from the endocardial border (Figure 3).³⁴ To facilitate comparison with tissue velocity variables from 2D echocardiography, the wall thickening velocity curves were defined so that normal systolic wall thickening gave positive velocities, and the diastolic wall thinning waves were negative.

Indices of systolic and diastolic function obtained by epicardial ultrasonic transducers

Systolic function was evaluated by measurement of wall thickness and wall thickening velocity. The wall thickness was obtained from the M-mode images, and the wall thickening velocities were measured from a reproducible subendocardial sample volume depth in all recordings, giving similar velocity patterns as known from 2D echocardiography tissue Doppler imaging (Figure 3). In the experimental studies the wall thickness was plotted against left ventricular pressure to generate pressure-wall thickness loops. The wall thickens during systole when the wall shortens in longitudinal and circumferential directions, thus the pressure-wall thickness loops revolved the opposite direction of conventional pressure-volume loops. The loop areas were calculated, and in the experimental studies these areas were used as a measure of systolic function (Study I and II).

The diastolic function of the myocardium depends partly on deactivation of active processes initiated during systole, and partly on passive LV properties, such as ventricular stiffness. In the early diastole the filling of the LV relies on rapid uncoupling of the myofibril bonds to let the LV cavity expand. This expansion normally occurs very swiftly and the volume is “sucked” from the atrium.³⁵ In late diastole the atrial contraction fills the LV to its end diastolic volume. In a normal ventricle the early filling dominates, but this mechanism is sensitive to changes in LV active or passive properties. During ischemia changes occur not only in the systole, but also in the diastole with the emergence of post-systolic contraction.¹⁵

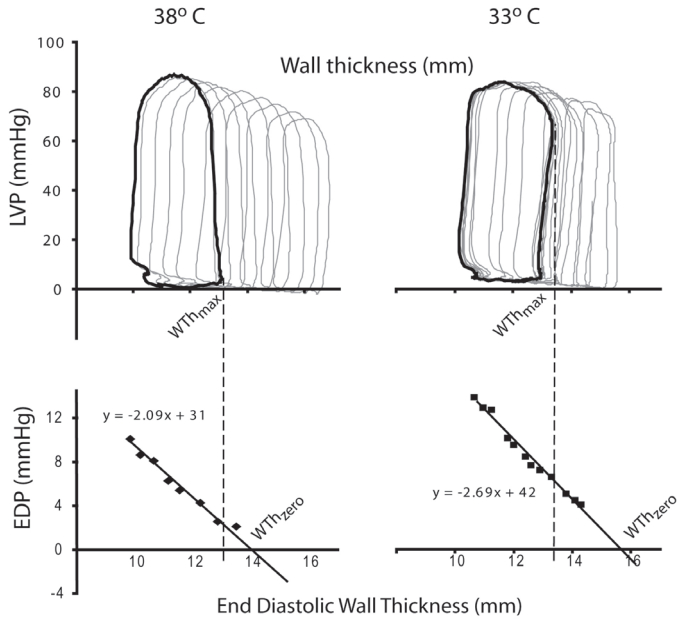


Figure 4. Pressure-wall dimension loops during caval constriction at spontaneous heart rate, demonstrating how the wall thickness increases while LV pressure decreases, producing loop series that decrease rightwards, opposed to leftward decrease in conventional pressure-volume loops. (From Espinoza et al. JASE manuscript)

In the studies on regional myocardial function (Study I and III) both systolic and post-systolic wall thickening velocities were assessed to discriminate regional from global changes in myocardial function. To obtain a more robust measure for ischemia detection a combined variable was constructed, incorporating both systolic and post-systolic wall thickening velocities. By subtracting systolic velocity from post-systolic velocity a resulting sum variable (V_{diff}) was obtained, to presumably obtain greater sensitivity and specificity in ischemia detection.

In study II the systolic and diastolic function during global LV function impairment from hypothermia was addressed. The early and late diastolic wall thinning and wall thinning velocities were measured using the epicardial M-mode recordings during

normothermia and hypothermia (Figure 5). Hypothermia *per se* induces a reduction in heart rate^{36,37}, so recordings were also made at a fixed heart rate induced by atrial pacing at 100 bpm to minimize effects in myocardial function due to heart rate differences. During atrial pacing at 33° C the diastolic early and late filling waves fused, and hence precluded analysis on early filling magnitude (e'). Early diastolic function was calculated as the early wall thinning fraction, defined as the wall thinning that occurred before the following P on ECG (Figure 5). This measure could be used in all situations.

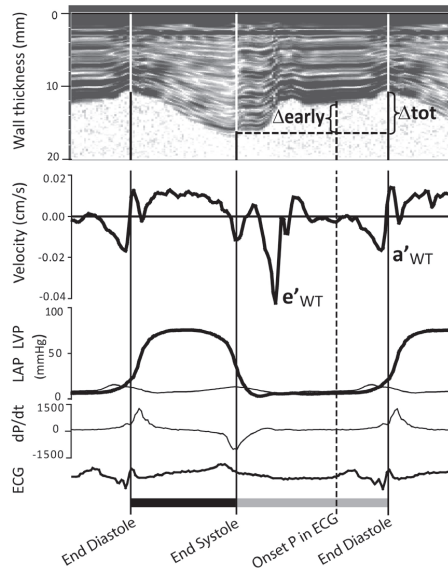


Figure 5. The upper panel shows a typical M-mode recording at baseline (38° C, spontaneous heart rate) with corresponding wall thickening velocities below, synchronized with pressure recordings (LVP and LAP), LV dP/dt and ECG in the lower panel. The solid vertical lines indicate end-diastole and end-systole. The horizontal black and grey bars at bottom indicate systolic and diastolic duration. The dashed vertical line indicates the onset of P in ECG. The early diastolic wall thinning (Δ early) was measured from maximum systolic wall thickness to onset of P, and divided by total diastolic wall thinning (Δ tot) to calculate the early diastolic wall thinning fraction. The early (e') and late (a') diastolic wall thinning waves are indicated. (Modified from Espinoza et al. JASE manuscript)

The relaxation of the LV starts after the peak LV pressure in the ejection phase and continues through the isovolumic relaxation phase (IVR). Since the volume of the ventricle is constant in the IVR, the rate of LV pressure decay in this phase is determined by the relaxation of the LV myocardium. The relaxation rate has been described as a contributor to reduced early diastolic function^{38,39}. The relaxation time constant (τ) was calculated by exponential fitting of the LV pressure curve in the IVR phase

$$(1) \quad P_{MVO} = P_{ES} e^{-k\tau + \beta}$$

where P_{ES} is the LV pressure at end-systole, and P_{MVO} is the LV pressure at mitral valve opening, with zero asymptote.⁴⁰ As the LV pressure curve in the IVR phase is described by an exponential function, the time for complete relaxation has been defined as 3.5 times the relaxation constant.⁴¹ This measure was used to investigate whether the duration of the diastole allowed complete relaxation by calculating time for complete relaxation as a fraction of diastolic duration ($3.5 \tau/DD$). In study II the pressure-wall thickness loops were also used to evaluate left ventricular diastolic function. During transient volume unloading by constriction of the inferior vena cava, pressure-wall thickness (P-WT) loops were plotted, the end-diastolic P-WT slope used as a measure of LV stiffness (Figure 4). Restoring force is an expression of the potential recoiling force of the myocardium after systolic compression. It can be envisioned as similar to compressing a spring coil, where the restoring forces are the outward, recoiling forces that works to re-establish the unstressed state of the spring coil, in this case the compressed myocardium. In study II we calculated restoring forces using the P-WT loops as basis for the calculations: The end-diastolic P-WT slope was extrapolated to LVP zero to obtain the unstressed wall-thickness. This wall-thickness was subtracted from the maximal wall-thickness during systole and the resulting distance was defined as the restoring forces (Figure 4). The end-diastolic P-WT relation during transient volume unloading was also used to determine LV stiffness.

Analyses of the epicardial transducer recordings and pressure recordings, including the pressure-wall thickness loops, were made using in-house developed analysis software (LabVIEW, National Instruments Corp, Texas, USA).

Automated signal analysis

Automated signal analysis would be a prerequisite for clinical use, hence in study II an algorithm was proposed. During ischemia changes in the wall motion occurs both in the systolic and in the post-systolic phase as a response to the LAD occlusion (S' and PSV in Figure 3). In the clinical study the velocity signal was integrated, resulting in a displacement curve similar to the wall thickening. Systolic wall thickening was obtained by automatically calculating displacement at end-systole, and this was calculated as a fraction of maximum displacement during the R-R interval. Lower fractions would be expected during ischemia, due to reduced systolic function and increase of post-systolic wall thickening. The R-peak in the ECG was automatically detected, and used as starting point in each cardiac cycle. Time of end-systole (T_{es}) was defined as 400 ms after R-peak.

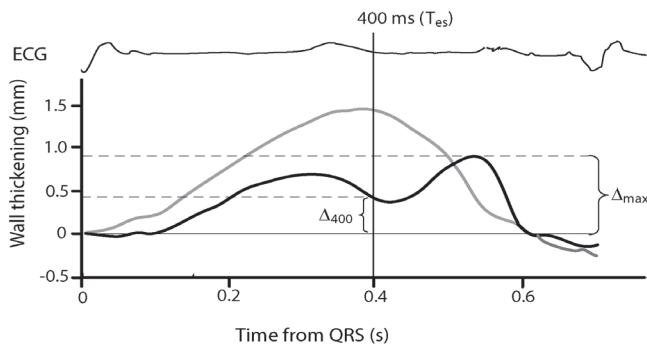


Figure 6. The displacement curves from the LAD (black) and reference (grey) regions are shown for one cardiac cycle, with ECG (top). Time of end systole (T_{es}) is indicated by the vertical line. The wall thickening at end systole (Δ_{400}) was registered and calculated as a fraction of maximal wall thickness in the cardiac cycle (Δ_{max}). For the LAD region the wall thickness at 400 ms and maximal displacement are shown as horizontal dashed lines. (From Espinoza et al. *Eur J Cardiothorac Surg* 2011 (39) 53-59)

Echocardiography

Two-dimensional (2D) echocardiography was used as a reference method to the recordings from the miniature epicardial ultrasound system. This method is the clinical gold standard for myocardial function assessment, and has been validated in several studies comparing this technique with sonomicrometric crystals and magnetic resonance imaging.^{14,42,43} Recordings were made using a Vivid 7 scanner (GE Vingmed Ultrasound AS, Horten, Norway). In the experimental studies a 2,5/2,75 MHz transducer was placed directly on the heart with a gel standoff. Recordings were obtained from the apex and from the anterior wall, providing two- and four-chamber projections, and short axis in basal, apical and mid-level. In the patient study a transesophageal transducer was used to obtain 2D grayscale recordings.

In the hypothermia study (Study II) the 2D echocardiography recordings were analyzed for left ventricle volume determination and transmitral flow recordings. The 2D echocardiographic longitudinal velocities and longitudinal strain from septal and lateral wall were used for reference. Midwall fractional shortening (mFS) was calculated according to deSimone et al.⁴⁴

$$(2) \quad mFS = \frac{(LVIDd + Hd/2) - (LVIDs + Hs/2)}{LVIDd + Hd/2}$$

End systolic wall stress was calculated as

$$(3) \quad (LVP * LVIDs/2) / 2Hs(1 + Hs/LVIDs).^{45}$$

LVIDd and LVIDs was the left ventricular inner diameter in end-diastole and end-systole respectively, whereas Hd and Hs was the average of anterior and posterior wall thickness at the same time-points.

The echocardiographic recordings were analyzed off-line (EchoPAC, GE Vingmed, Horten, Norway), using tissue Doppler and speckle tracking echocardiography to obtain myocardial velocities and strain values from the regions of interest. Ischemia was defined as a reduction in longitudinal strain >30%.

Hemodynamic measurements

In the experimental studies the pressure recordings from the left ventricle (and atrium in study II) were obtained by micromanometers (MPC-500, Millar Instruments, Texas, USA). Peak LV pressure and end-diastolic pressures were recorded. Time derivative of LV pressure (dP/dt) was calculated and dP/dt_{\max} recorded. In study II the LV pressure curve was used to determine the LV relaxation constant. ECG was obtained from the analogue output channel from a Siemens SC 900XL monitor (Siemens AG, Erlangen, Germany); the filtering delay through the monitor of 22 ms was compensated. Using a synchronizing signal the ECG signal and pressure recordings were synchronized with the ultrasound measurements. Cardiac output was recorded by transit time flow probe on the aorta.

In the clinical study the arterial pressure and ECG were obtained from the patient monitor, and displayed together with the ultrasound measurements, while cardiac output was measured by transthoracic thermodilution (PiCCO 5.1, Pulsion Medical Systems AG, Munich Germany).

Statistical analyses

The subjects in the studies served as their own controls. Comparisons between baseline and interventions were made using paired T-test. The relation between test and reference methods in study I was analyzed using mixed model analysis. Sensitivity and specificity for regional function assessment were calculated by ROC curves and 2x2 table analysis (study I and III). In study II and III the repeated measurements were analyzed using linear mixed models with random intercept to handle the dependencies introduced by repeated measurements within each subject. In study II temperature and heart rate were used as determinants, and time of recording included as a covariate to account for the order of measurements. Further, determinants for early diastolic function were assessed. Model selection was made choosing the covariance structure with the lowest Akaike information criteria. Differences were considered significant if $P < 0.05$.

Summary of results

Paper I

The aim of this study was to test and validate the use of epicardial transducers to continuously monitor left ventricular myocardial function, and to detect regional function changes induced by coronary occlusion and discriminate these from global function changes. During LAD occlusion there was an instantaneous reduction in myocardial velocity with increase in post-systolic velocity in the interventional region (Figure 3). No changes in either part of the signal occurred in the reference region. Subsequent reduction in LAD flow 50% induced smaller changes in motion pattern, increasing when proceeding to full occlusion. During LAD occlusion the pressure-wall thickness loop in the interventional region changed direction, and the resulting loop area became negative, indicating paradox myocardial motion in this region. LVP decreased during LAD occlusion, while EDP increased. CO remained unchanged.

During global interventions by beta-adrenergic stimulation and inhibition, and volume challenge/unloading the changes were similar in the two regions of the left ventricle. There was an increase in systolic wall thickening velocity with adrenergic stimulation, and reduction during beta-adrenergic blocking, whereas volume interventions induced no changes. No alterations occurred in post-systole in either region during the global interventions. Hemodynamic variables (LVP, CO and dp/dt_{max}) increased with adrenaline stimulation, whereas these variables decreased during esmolol infusion. Increase in LV volume load increased hemodynamic variables, whereas LVP decreased during nitroprusside infusion.

The epicardial transducer system was able to detect regional myocardial function impairment equally good as 2D echocardiography, and could discriminate regional from global changes with high sensitivity and specificity.

Paper II

The aim of this study was to assess the changes in systolic and diastolic function during hypothermia using 2D echocardiography and the epicardial ultrasound system.

Hypothermia induced no apparent changes in LV function as assessed by clinical routine ultrasonographic methods, such as stroke volume, end diastolic volumes or wall dimensions. 2D echocardiography longitudinal strain and midwall fractional shortening also remained unchanged during hypothermia. However, the similar LV deformation and stroke volume during hypothermia occurred during a prolonged systole, thus the rate of systolic change was reduced. These findings were confirmed by significant decreases in wall thickening velocity and 2D longitudinal shortening velocity.

The wall thickening velocity was reduced similarly at both spontaneous and paced heart rates during hypothermia, while the deformation measures remained unchanged at spontaneous heart rate. The rate of deformation thus seemed less preload dependent than the magnitude of deformation in this situation. Even though the stroke volume and deformation was preserved, this occurred at lower generated pressure and thus reduced wall stress. The reduction in myocardial work was confirmed by the reduction of pressure-wall thickness loop areas.

Early diastolic function was reduced during hypothermia, with a shift from early to late diastolic filling and reduced early longitudinal lengthening and diastolic wall thinning velocities (Figure 7). Due to the prolonged systole the diastolic duration as fraction of the cardiac cycle was shortened. The relaxation constant (τ) was prolonged at 33°C. The time for complete relaxation (3.5τ) was within the duration of diastole during spontaneous heart rate at 38° and 33°C, and during paced heart rate at 38°C. When pacing at 33°C, however, the time for complete relaxation exceeded diastolic duration. The P-WTh loop analyses demonstrated increased LV stiffness and reduced restoring forces. These changes were temperature dependent, with no effect from increased heart rate. The relaxation constant and the LV stiffness proved to be significant contributors to decreased early diastolic function during hypothermia. In summary this study demonstrated that moderate hypothermia induces systolic and diastolic dysfunction as measured by 2D echocardiography and epicardial M-mode recordings. The early diastolic dysfunction was dependent on delayed relaxation and increased LV stiffness, and lessened the tolerance to increased heart rates.

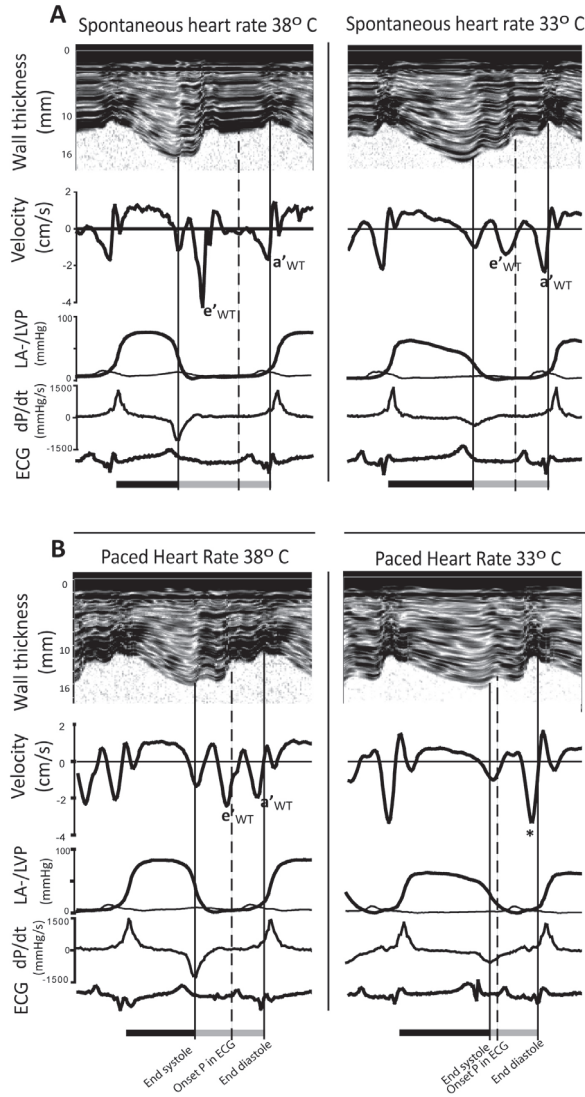


Figure 7. Recordings from spontaneous heart rate and atrial pacing at 38°C and 33°C. The vertical solid lines indicate the end-systole and end-diastole, while the vertical dashed lines marks the onset of P-wave on ECG. The bars below show the duration of systole (black) and diastole (grey), with shortened diastolic duration during both pacing and hypothermia. Pacing at 33°C caused fusion of the e' and a' waves (*). (Modified from Espinoza et al. JASE manuscript)

Paper III

The aim of this study was to validate the ultrasound system in patients, and to validate a proposed algorithm for automated signal analysis. During the 60 s trial occlusion before LAD grafting, ischemia was confirmed by 2D echocardiography in 9 of 10 patients, while no significant change occurred in conventional monitoring variables (MAP, heart rate, CO, ECG ST segment). Systolic wall thickening velocity was significantly reduced in these 9 patients, with concomitant increase in post-systolic wall thickening velocity. The V_{diff} - incorporating changes in both systole and post-systole - changed from positive to negative values in the patients with confirmed ischemia. In contrast to systolic and post-systolic velocities the V_{diff} values during LAD occlusion did not overlap with the baseline values.

When the LAD vessel was occluded for grafting a reduction in systolic wall thickening velocity occurred in all nine patients with confirmed ischemia, and only in the LAD region. Post-systolic velocity increased, and the resulting V_{diff} changed from positive to negative in all nine patients. During grafting the V_{diff} values in the LAD region for the patients with intracoronary shunt differed significantly from the patients who were grafted without shunt, and normalized after completed grafting in all patients (Figure 8). No significant changes in hemodynamics or ECG occurred during grafting.

The automated signal analysis algorithm detected a significant change in systolic wall thickening in the interventional region during the trial occlusion, with good sensitivity and specificity. During grafting there was a similar significant reduction in the systolic wall thickening fraction, with complete restoration after completed LAD grafting.

In summary we demonstrated that the ultrasonic system could detect myocardial ischemia with high sensitivity and specificity in patients undergoing coronary bypass surgery. Combining systolic and post-systolic changes during ischemia increased sensitivity and specificity. The proposed automated signal analysis algorithm, incorporating systolic and post-systolic changes, was able to identify ischemia.

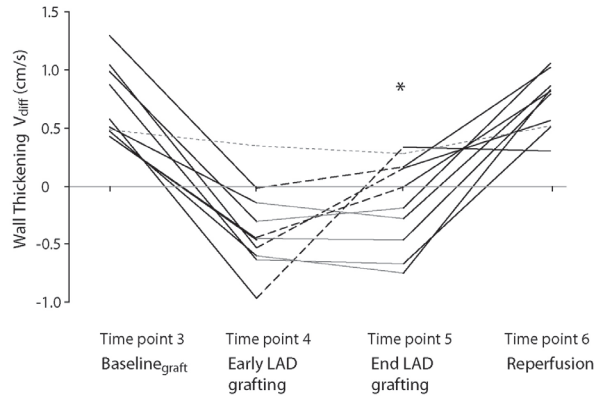


Figure 8. The velocity difference (V_{diff}) in the LAD region was calculated as ($S'-PSV$) and displayed for each patient during LAD grafting. There was a significant decrease from Baseline to early LAD grafting. The dashed lines during LAD occlusion (time points 4 – 5) show increase in V_{diff} in the patients in the intracoronary shunt group. The solid lines in the same interval represent the patients in the no-shunt group. The difference between the groups was significant at time point 5 (*). The short-dashed line shows the patient who did not develop ischemia. (From Espinoza et al. *Eur J Cardiothorac Surg* 2011(39):53-59)

Discussion

In this work an ultrasonic system with epicardial transducers for monitoring of myocardial function has been provided and validated. Transducers fixated to the epicardium were used to obtain signals that produced an M-mode image with synchronous presentation of wall thickening velocities. The ultrasound system enabled continuous and real-time assessment of systolic and diastolic function, and the signals could be used in combination with LV pressure to provide more advanced indices of myocardial function. The system could detect changes in regional and global myocardial performance, and discriminate between these with excellent sensitivity in both experimental and clinical studies. Automated signal analysis proved feasible in regional function impairment detection, and performed equally sensitive as manual off-line analysis.

Systolic and diastolic function assessment

Systolic function indices

The contraction pattern of the myocardium can be described by various indices. In conventional 2D echocardiography the regional myocardial function has been graded by use of a visual wall motion score.⁴⁶ With the emergence of more advanced imaging techniques; myocardial motion variables such as acceleration, velocity and displacement have all been investigated for assessment of systolic function.⁴⁷⁻⁴⁹ The epicardial ultrasound system used in this project produced M-mode images that allowed assessment of all these variables. However, to obtain a measure that could provide a continuous estimate of the myocardial function, the wall thickening velocity was chosen. The reason for this was the familiarity with tissue velocities described in studies using tissue Doppler imaging or strain echocardiography techniques, and because this would obviate algorithms for automated border detection to enable continuous dimension measurements. The regional tissue velocity has been demonstrated to give very good information on the function^{15,50}, and has also proved robust when measured by use of other methods such as the epicardial accelerometer.⁴⁸ The transmural wall dimension changes have been used from the early echocardiography era (M-mode images), and has also been investigated by use of sonomicrometric crystals. The wall

thickening changes have been shown to correlate inversely with segment lengthening and end-diastolic diameter, and to correlate well with global changes.⁵¹

The pressure-wall dimension loops describe the regional myocardial work as they incorporate both the LV pressure increase and the dimension change of the myocardium, and reflect the myocardial oxygen consumption.^{52,53} The principle of plotting wall-thickness against left ventricular pressure as a measure of regional myocardial work has been used previously to define the regional contractile state during coronary stenosis and occlusion.^{54,55}

During LAD occlusion (study I) the direction of the loop was reversed, resulting in a negative loop area typical of paradox movement seen during ischemia.⁵⁶ During systole less or no force is exerted by the ischemic myocardium, hence this part of the myocardium is stretched due to the force of the cavitory pressure and the active contraction of the neighboring segments. This is followed by a late-systolic or post-systolic segment shortening. During ischemia this results in lesser wall thickening or even wall thinning during systole, followed by increased post-systolic wall thickness. The latter phenomenon is found to be composed of passive-elastic recoil after stretch, and a component of active contraction.⁵⁶ In our studies we did not address this latter point, but the pressure-wall thickness loops demonstrated the typical ischemic changes with reversal of loop direction and reduction in area.

In study II the pressure-wall thickness loop area was reduced during intervention, demonstrating a reduction in regional myocardial work, dependent on reduced LV pressure generation. Several studies have assessed the myocardial function during hypothermia, and it is remarkable how the effects on systolic function vary. Studies have demonstrated an increase in systolic function assessed by dp/dt_{max} ⁵⁷, end-systolic pressure-dimension relationship (E_{max})^{58,59}, or regional work represented by pressure-dimension loop area⁵⁹, whereas other studies have not been able to demonstrate any change^{37,58,60,61}, or even have demonstrated a reduction in systolic function during hypothermia as measured by these variables.^{28,37,57-63} The findings in these studies may reflect on differences in study design regarding level of temperature, control of heart rate, or differences in anaesthesia or hemodynamic management; all of which could

have influence on preload, afterload and contractility, and thereby on the overall function of the LV.

The moderate level of hypothermia in study II induced no apparent changes in global LV function concerning stroke volume, end-systolic and -diastolic volumes or longitudinal strain values. However the afterload was reduced so the contractile force exerted was reduced, and the systolic velocity was diminished during hypothermia. The latter reflected the fact that similar displacement took place in a prolonged systole. The changes observed by 2D echocardiography were demonstrated also by the epicardial transducers. The same wall thickening occurred within the longer systole; hence the wall thickening velocity was reduced. Because of the decreased LVP the regional work was reduced as assessed by pressure-wall dimension loops.

Diastolic function indices

The early diastolic function of the left ventricle is dependent on the cessation of the systole. If the uncoupling of the myofibril bonds between the contractile elements is delayed or unsynchronized, this prolongs the relaxation phase. Diastolic dysfunction may therefore appear from different causes, such as ventricular hypertrophy, ischemia, or hypothermia.

During ischemia there is an attenuated systolic function, but a post-systolic contraction appears after the end systole. The ischemic region acts out of phase with the remainder of the ventricle, and due to contraction in the late systole and early diastole contributes to impediment of the global early diastolic function.⁶⁵ This impedes the diastolic intraventricular pressure gradient, and delays LV filling.⁶⁶ In study I diastolic function was affected by the emergence of post-systolic wall thickening, and reduced early diastolic wall thinning was observed (Figure 3).

In study II the hypothermia affected diastolic function. In the literature the changes in diastolic function are more uniform than the findings on systolic function. Prolongation of the relaxation constant is one of the most consistent findings.^{28,37,57-63} In Study II we found prolonged relaxation constant during hypothermia, and the relaxation constant was associated with delayed wall thinning. Together with change in LV stiffness and decrease in restoring forces, the resulting diastolic dysfunction resulted in a shift from

predominantly early diastolic filling to late filling, as assessed by transmitral flow. This finding was in accordance with a similar change, with severely delayed wall thinning pattern as assessed by M-mode imaging by the epicardial transducers.

Tachycardia has been demonstrated to affect LV filling. If the heart rate is too rapid the diastolic duration is reduced to an extent where there is not sufficient time for complete diastolic filling.⁶⁷ This can be considered together with the rate of relaxation. According to Weisfeldt et al. the time required for complete relaxation can be calculated as 3,5 times the relaxation constant (τ).⁴¹ If the heart rate increases the diastole will at some point not give enough time to complete relaxation. If the relaxation constant for some reason is prolonged so will the 3,5 τ also be, adding to the challenge of completing the relaxation within the diastolic duration. In the hypothermic model, this phenomenon was demonstrated when the heart rate was increased by atrial pacing at 100 bpm during hypothermia. The stroke volume was then reduced, while at normothermia the stroke volume was maintained during pacing compared to spontaneous heart rate. A similar response has been described in patients with heart failure with preserved ejection fraction, or diastolic heart failure. In these patients, having prolonged relaxation and increased LV stiffness at baseline, the stroke volume was demonstrated to be reduced during pacing-induced increase in heart rate.⁶⁸ This was found by the M-mode images to coincide with an increase in end-diastolic wall thickness and reduced end-systolic wall thickness.

2D echocardiography is, in addition to routine hemodynamic monitoring, the principal modality for bedside assessment of cardiac function. The aim of study II was therefore to describe the changes in myocardial systolic and diastolic performance during hypothermia by use of ultrasound imaging techniques. The changes observed by use of the epicardial transducers were in accordance with the results obtained by conventional and more advanced imaging techniques using 2D echocardiography. The increase in systolic duration together with reduction in spontaneous heart rate we found in our study were in accordance with previous findings.^{36,37,57} The effects on systolic and diastolic function were not dependent on the order of interventions, so that when the hypothermic measurements were performed first, the observed effects returned to “normal” values when the animals were warmed. Other studies on myocardial function

during hypothermia support the assumption that the reduced systolic function recovers – at least partially – upon rewarming.⁶⁴ In a recent study the animals were exposed to a lesser degree of hypothermia (25°C). The systolic function partially recovered, and diastolic function recovered completely.⁶⁰ In clinical situations the deterioration of systolic cardiac function during hypothermia may include effects from the temperature *per se*, and thus myocardial function assessment by echocardiography should be interpreted cautiously.

Regional vs. global assessment

The use of the epicardial transducers to monitor myocardial function gives information from the region where they are fixated. Hence, more than one transducer is required if the aim is to discriminate between regional and global function changes, as demonstrated in studies I and III. In case of global changes in cardiac function, the altered function will be discovered by both or all of the transducers. In study I the changes in myocardial velocity increased during epinephrine infusion, and decreased during beta-blocker administration. During altered loading conditions there was no change in wall thickening velocity, in spite of increased or decreased blood pressure and cardiac output. During LAD occlusion the regional changes were detected rapidly, and with high sensitivity. The transmural velocity thus appears to be an excellent index for contractile function, but not very sensitive for detecting changes in preload.

In study II the wall dimension recordings from the epicardial transducers were obtained regionally, but assumed to represent global changes. The changes in diastolic wall thinning velocity (e' and a') changed similarly to the transmitral flow velocities, the midwall fractional shortening and longitudinal strain obtained by 2D echo/Doppler recordings. The regional performance have been demonstrated previously to reflect the global changes, as different segments of the LV behave similarly during global changes.¹²

In study I the global interventions induced altered systolic velocities in both regions investigated, whereas LAD occlusion induced changes only in the region supplied by LAD. The reduction in systolic wall thickening velocity induced by LAD occlusion did

not overlap with the velocities in baseline recordings or the velocities during any of the global interventions.

In the patient study the sensitivity for systolic velocity alone was not as good for detection of ischemia in this setting as in the experimental study. This could be due to pre-existing coronary disease and developed collateral circulation that supplied parts of the area at risk. The LAD occlusion induced changes in both the systolic and the post-systolic phase. The consideration of both phases has been demonstrated to increase the sensitivity in ischemia detection^{15,49,69} therefore a combined index (V_{diff}) was validated in the patient study. By using the V_{diff} the sensitivity increased, and there was no overlap between baseline and interventional recordings.

Interestingly, in the clinical study the patients could be divided in two groups, those who received intracoronary shunt during IMA-to-LAD grafting and those who did not. The study was not designed to investigate subgroups at this level, but the groups did differ when analyzed by mixed model analysis. At the end of grafting, just before removal of shunt in the shunt group, or before completion of anastomosis in the no-shunt group, there was significant difference between the groups (Figure 8). Hence, continuous monitoring provided important information of myocardial function during the procedure, and confirmed good shunt function in all patients. The continuous monitoring during different phases of cardiac surgery may assist the interpretation of the hemodynamic changes, or even reveal dysfunction that is otherwise undetected in crucial steps of cardiac surgery procedures, such as weaning from cardiopulmonary bypass. We observed two episodes of myocardial dysfunction during wide sternal retraction during OPCAB procedures.⁷⁰ Recognition of the problem was aided by the ultrasound transducers, and corrective measures could be taken early, as myocardial motion improved upon easing the sternal retractor.

Automated signal analysis

The principle of incorporating systolic and post-systolic changes into one variable was also applied to the automated signal analysis algorithm in study II, where the systolic wall thickening was calculated as a fraction of the total wall thickening in the cardiac

cycle. In baseline situations most of the wall thickening occurs in the systole, whereas in ischemic situations a substantial part of the wall thickening occurs late or even after end-systole. The use of this automated algorithm allowed identification of ischemic changes during LAD occlusion in patients with excellent sensitivity and specificity.

The use of both systolic and post-systolic signal changes increases the sensitivity. It does, however, introduce a challenge in timing of end-systole based on the clinically available variables (M-mode, ECG, arterial pressure). The method used in study II of using a fixed interval of 400 ms from R on ECG will be inaccurate when greater variations in heart rate occur. A frequency-correction, along the principle of corrected QT time, would reduce the inaccuracy.

The use of automated algorithms has been tested using various methods for image analysis in 2D echocardiography. The border tracking algorithms detect the outer and inner rim of the myocardium, thereby providing a method to estimate myocardial thickening/thinning and shortening/lengthening during the cardiac cycle.⁷¹ An application for automated motion analysis using strain rate analysis has also been developed, using a combination of speckle tracking echocardiography with tissue Doppler technique to assess the segmental deformation of the myocardium.⁷² Even though the described techniques perform well in these studies, they depend on post-hoc analysis of the echocardiographic recordings. This makes immediate bedside use cumbersome, and relies on a skilled operator to acquire and analyze the recordings. The technique proposed in study III allows real-time analysis of the signal; hence it represents a potential principle for clinical application.

An earlier version of a single-crystal system has been tested previously. This technique did not present images, sample volume depth was aided by audio signal, and wall thickening was estimated by integration of the obtained signal. Although measurements provided good estimates of wall thickening changes, the technique was cumbersome and impractical for clinical use.²¹ This version was however also tested in patients.⁷³

The new system represents an improvement both in signal presentation and with potential for real-time automated signal analysis. This provides possibility for immediate detection of adverse events, and early possibility for possible corrective

measures. Newer applications, such as simultaneous multi-layer analysis of the myocardial wall, are currently explored.

Limitations

The uniformity of regional myocardial function in the non-ischemic heart has been reported previously.^{12,74} In the study on global cardiac function, the extrapolation of regional measurements relies on the changes being similar in all regions of the left ventricle. The described ultrasound system monitored limited volumes of the LV wall, but from the exact same region throughout the experiments. Even though there may be differences in the response in different regions of the left ventricle, the region in scrutiny served as its own control. The changes due to global challenges behaved similarly in regional and global measurements (study I and II); hence global uniformity in changes were assumed in study III. This assumption was supported by the similarity in wall thickness analysis vs. transmitral flow measurements.

The monitoring volume of the described transducers is limited. Although the monitored area extends to some degree outside the area covered by the transducers due to tethering, the transducers provide a regional measure. A three-axis accelerometer recently developed is more sensitive to tethering effects, and therefore picks up remote changes to a greater extent than the epicardial ultrasound transducers. However, regional function impairment as ischemia is detected with better sensitivity by the ultrasound technique. Global monitoring will still rely on the use of more than one transducer to pick up regional changes. The transducers used in these studies still need miniaturizing to be clinically applicable for monitoring extending into the postoperative phase. That requires small transducers that allow percutaneous removal. There are commercially available transducers today that are substantially smaller than the prototypes used in the present studies, making postoperative use feasible. However, the present transducers are small enough for extended use, in case of permanent monitoring together with implanted devices such as cardiac resynchronization pacemakers or ventricular assist devices.

The implantation of the described sensors require open placement during surgery, and precludes use in the non-surgical setting. This limits the use of such a sensor system at present. However, the development in recent years has produced very small ultrasound

sensors, among them sensors for intravascular use. Along with the pace of technological progress the advent of small ultrasound transducers suitable for transvascular placement is realistic in near future. The accelerometer sensors mentioned above may be even easier to develop for this purpose.⁴⁸

Future perspectives

As the number of patients with heart failure is increasing, the number of patients receiving ventricular assist devices as bridge to cardiac transplant will probably also rise.⁷⁵ The emerging use of implantable monitoring devices to monitor heart failure patients demonstrates the increased attention these patients receive in order to reduce mortality and morbidity. Techniques such as intrathoracic impedance and implantable hemodynamic monitoring (IHM) devices are in development to better adjust therapy in future heart failure patients, hopefully to avoid hospitalization. Both the impedance system and the IHM systems are currently investigated for their ability to predict exacerbations in heart failure, and whether therapy guided by these systems can reduce morbidity and mortality.^{76,77} In this context it may be that a developed version of the ultrasonic system could give valuable information in both the vulnerable perioperative phase, but also in the long-term management of these patients.

It is likely that future systems will not only utilize indirect measures of cardiac function, but also will incorporate direct measures on myocardial performance. The use of automated myocardial motion assessment algorithms will necessarily have to develop as a result of this. Hopefully, the present work can provide a contribution in the construction of such future systems.

Conclusions

1. We have through these studies provided an ultrasonic system, with miniature ultrasonic transducers for fixation on the heart, which can give continuous real-time assessment of regional myocardial performance.
2. The system could provide assessment on systolic and diastolic function. The obtained signals may discriminate between global and regional changes, and ischemic changes can be detected with high sensitivity and specificity.
3. The system was tested for its feasibility in a clinical setting, and demonstrated excellent ability to detect ischemia in patients with pre-existing coronary disease.
4. An algorithm for automated ischemia detection was proposed and validated, demonstrating good ability to detect regional function impairment during coronary occlusion.
5. The system has also been used to obtain myocardial function assessment in an experimental study on hypothermia at a clinically relevant level. The technique was used to gain insight in the LV systolic and diastolic dysfunction during moderate hypothermia. These findings may have implications for management of patients undergoing hypothermia as part of the treatment.

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